BQ (16)

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 9/10 — A1

(11) International Publication Number: WO 00/21504

(43) International Publication Date: 20 April 2000 (20.04.00)

(21) International Application Number: PCT/US99/20905

(22) International Filing Date: 6 October 1999 (06.10.99)

(30) Priority Data:

60/103,700	9 October 1998 (09.10.98)	US
60/109,696	24 November 1998 (24.11.98)	US
09/233,443	20 January 1999 (20.01.99)	US

(71) Applicant *(for all designated States except US)*: GENERAL MILLS, INC. [–/US]; Number One General Mills Boulevard, Minneapolis, MN 55426 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: VAN LENGERICH, Bernhard, H. [DE/US]; 18005 33rd Place N., Plymouth, MN 55447 (US).

(74) Agent: TAYLOR, Douglas, J.; General Mills, Inc., P.O. Box 1113, Minneapolis, MN 55440 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.
With amended claims.

(54) Title: ENCAPSULATION OF SENSITIVE LIQUID COMPONENTS INTO A MATRIX TO OBTAIN DISCRETE SHELF–STABLE PARTICLES

(57) Abstract

A liquid encapsulant component which contains an active, sensitive encapsulant, such as a live microorganism or an enzyme dissolved or dispersed in a liquid plasticizer is admixed with a plasticizable matrix material. The matrix material is plasticizable by the liquid plasticizer and the encapsulation of the active encapsulant is accomplished at a low temperature and under low shear conditions. The active component is encapsulated and/or embedded in the plasticizable matrix component or material in a continuous process to produce discrete, solid particles. The liquid content of the liquid encapsulant component provides substantially all or completely all of the liquid plasticizer needed to plasticize the matrix component to obtain a formable, extrudable, cuttable, mixture or dough. Removal of liquid plasticizer prior to extrusion is not needed to adjust the viscosity of the mixture for formability. Release of an active component from the matrix may be delayed or controlled over time so that the active component is delivered when and where it is needed to perform its intended function. Controlled release, discrete, solid particles which contain an encapsulated and/or embedded component such as a heat sensitive or readily oxidizable pharmaceutically, biologically, or nutritionally active component are continuously produced without substantial destruction of the matrix material or encapsulant.

ENCAPSULATION OF SENSITIVE LIQUID COMPONENTS INTO A MATRIX TO OBTAIN DISCRETE SHELF-STABLE PARTICLES

FIELD OF THE INVENTION

The present invention relates to a continuous process for producing shelf-stable, controlled release, discrete, solid particles from a liquid encapsulant component which contains a sensitive encapsulant, such as a heat sensitive or readily oxidizable pharmaceutically, biologically, or nutritionally active component.

BACKGROUND OF THE INVENTION

In encapsulating a component in a matrix, the matrix material is generally heated to a sufficiently high temperature to provide a plasticized mass which facilitates embedding or coating of the component. Upon cooling, the matrix material hardens or becomes solidified and protects the encapsulant from undesirable or premature reaction. However, heating of the matrix to plasticize it or to form a melt may deleteriously affect or decompose the encapsulant as well as the matrix material. Additionally, the mixing or high shear used to disperse the encapsulant uniformly throughout the plasticized matrix material may likewise adversely affect the matrix material or encapsulant. Furthermore, the use of high temperatures to plasticize or melt the matrix material may cause evaporation and loss of the encapsulant. The addition of liquids to the matrix material to reduce its viscosity and to facilitate mixing may require excessive drying or evaporation of the plasticizing liquid for the attainment of a formable composition capable of being formed into discrete, substantially uniform pieces. Furthermore, removal of the plasticizing liquid may adversely expand the product, decrease its density, and make the encapsulated component more susceptible to attack or more easily released. These problems involved with the removal of liquid encapsulant are even more pronounced when the commercially available form of the encapsulant is dissolved or dispersed in a liquid. While the liquid may be removed prior to encapsulation by drying, expensive methods such as spray drying, freeze drying, and vacuum drying are generally needed to avoid decomposition of the encapsulant by drying at elevated temperatures. Additionally, the dried

encapsulants may be dusty and may cause adverse health effects when handled in concentrated forms or when inhaled.

The production of expanded products is disclosed in European patent publication nos. EP 0465364 A1 (published January 8, 1992) and EP 0462012 A2 (published December 18, 1991), U. S. patent no. 3,962,416 to Katzen and U. S. patent no. 3,786,123 to Katzen. The two European patent publications disclose the production of an anti-obesity food and a method for making it by extrusion of starches with fatty acids into an expanded product having densities between 0.1 and 0.3 g/cm^3. U. S. patent no. 3,962,416 to Katzen discloses an expanded product which contains at least one nutrient and one gelatinized starch.

U. S. patent no. 3,786,123 to Katzen discloses a method for producing encapsulated nutrients using extrusion temperatures of between 250°F and 400°F and extrusion pressures of between 200 psi to 2500 psi. A high protein encapsulating agent containing up to 40% starch may be used. The starch is gelatinized and extruded into an expanded product.

However, in producing a product having controlled release or delayed release, excessive expansion or puffing may result in too rapid release properties or may undesirably expose an encapsulant to destructive reactions. For example, an edible composition for delivering encapsulated pharmaceutically or nutritionally active components or for a non-edible agricultural product for delivering biocides or herbicides, it is desirable that the products have a substantially spherical shape and a high density. Such products exhibit a substantially low ratio between surface area and volume and thus minimize or prevent surface related destructive reactions that occur upon exposure to air or oxygen and light. The spherical shapes and high densities also minimize the surface which would be available to expose embedded material which is not encapsulated. Furthermore, for edible products for delivering pharmaceutically or nutritionally active components, it is desirable that the products are capable of being consumed or swallowed without chewing or substantially no chewing. Avoiding the need for mastication, further assures that the products reach the

encapsulants may be dusty and may cause adverse health effects when handled in concentrated forms or when inhaled.

The production of expanded products is disclosed in European patent publication nos. EP 0465364 A1 (published January 8, 1992) and EP 0462012 A2 (published December 18, 1991), U. S. patent no. 3,962,416 to Katzen and U. S. patent no. 3,786,123 to Katzen. The two European patent publications disclose the production of an anti-obesity food and a method for making it by extrusion of starches with fatty acids into an expanded product having densities between 0.1 and 0.3 g/cm^3. U. S. patent no. 3,962,416 to Katzen discloses an expanded product which contains at least one nutrient and one gelatinized starch.

U. S. patent no. 3,786,123 to Katzen discloses a method for producing encapsulated nutrients using extrusion temperatures of between 250°F and 400°F and extrusion pressures of between 200 psi to 2500 psi. A high protein encapsulating agent containing up to 40% starch may be used. The starch is gelatinized and extruded into an expanded product.

However, in producing a product having controlled release or delayed release, excessive expansion or puffing may result in too rapid release properties or may undesirably expose an encapsulant to destructive reactions. For example, an edible composition for delivering encapsulated pharmaceutically or nutritionally active components or for a non-edible agricultural product for delivering biocides or herbicides, it is desirable that the products have a substantially spherical shape and a high density. Such products exhibit a substantially low ratio between surface area and volume and thus minimize or prevent surface related destructive reactions that occur upon exposure to air or oxygen and light. The spherical shapes and high densities also minimize the surface which would be available to expose embedded material which is not encapsulated. Furthermore, for edible products for delivering pharmaceutically or nutritionally active components, it is desirable that the products are capable of being consumed or swallowed without chewing or substantially no chewing. Avoiding the need for mastication, further assures that the products reach the

digestive tract without substantial enzymatic hydrolysis in the mouth. Furthermore, it helps to control or reduce dissolution of the product in gastric juice and to control the release of the embedded or encapsulated components in the stomach and/or in the intestine.

International patent publication no. WO 92/00130 (published January 9, 1992) discloses a continuous process for obtaining an encapsulated, biologically active product in a starchy matrix. A biologically active agent and starch are mixed before extrusion and extruded as a blend, with the encapsulant or biologically active agent being heated together with the starch. Alternatively, a core material to be encapsulated may be added and blended with an aqueous dispersion of starch after the starch and water have been subjected to an elevated temperature sufficient to gelatinize the starch. The extrusion process, it is disclosed, exposes the mix to high shear mechanical action at a temperature above the gelatinization temperature of the starch. The use of extrusion barrel temperatures of between about 58°C and 98°C are disclosed. While these barrel temperatures may be above the gelatinization temperature of starch, the extruder utilized has barrel sections that are only three l/d long. The screw speeds utilized, between 400 rpm and 200 rpm, result in a very short residence time of the blend inside the extruder and barely allow heating up of the starch water mix. As a result, the temperatures obtained are generally too low to obtain substantial gelatinization of native starches. Additionally, the barrel temperatures used are particularly too low for substantial gelatinization of high amylose starch which generally gelatinizes at temperatures substantially above 100°C, for example at 125°C. The use of extrusion barrel temperatures which are not sufficiently high to substantially or completely gelatinize the starch may not form a sufficiently continuous, plasticized and homogeneous matrix for effective embedding or encapsulation.

In addition, the use of relatively low extrusion temperatures, high speed mixing, and a high viscosity starch composition generally requires a high mechanical energy input. High shear is directly related to high specific

mechanical energy, which in turn increases the molecular destructurization and dextrinization of starch. Breakdown of the starch molecules, and in particular the amylopectin, increases the solubility of the extruded starch composition in aqueous systems as described in P. Colonna, et al., "Extrusion Cooking of Starch & Starchy Products," Extrusion Cooking, C. Mercier, et al. pp. 247-319, AACC, St. Paul, Minn. (1989) and F. Meuser, et al, "A Systems Analytical Approach To Extrusion," Food Extrusion Science & Technology, ed. J. Kokini, Dekker Publ., pp. 619-630 (1992). Increased solubility of the extruded starch in aqueous systems decreases the stability of the product against moisture and subsequently diminishes or shortens the protection and controlled release of the embedded or encapsulated substances. In addition, subjecting the encapsulant to the same high shear and high temperature conditions to which the starch is subjected may adversely affect the encapsulant by at least partially destroying it or decomposing it into unknown solid or volatile substances.

Pregelatinized starch is used in numerous applications in the food industry as a swelling agent and for accelerated and extended water absorption in foods such as soups, sauces, instant puddings, baby food, and thickening agents. However, it has been found that the use of pregelatinized starch or the use of starch as the only matrix material during extrusion cooking generally results in a matrix which releases the encapsulant too quickly. It has been found that the penetration of water into a pure starch matrix causes early release of the encapsulant into the environment. Generally the time to release 100% of the encapsulant is too short to provide a desirable time-release or controlled-release which is effective for delivering the encapsulant at a desired location or time.

International patent publication no. WO 95/26752 (published October 12, 1995) discloses the production of a food product for the enteric supply of a fatty acid, a fatty acid containing substance, an amino acid, or an amino acid containing substance by at least partially complexing the fatty acid or amino acid in the amylose helix of starch to mask the acid. The product may contain one or more flavors and colors, fat soluble substances, anti-oxidants, or pharmacologically

effective substances. The components may be first dry mixed and subsequently fed into an extruder where they are substantially mixed and subsequently heated above the gelatinization temperature of the starch to obtain an elasticized mass which is extruded and formed into pellets. However, heat-sensitive components would be destroyed during the heating step.

International patent publication no. WO 85/04074 to Flashinski, et al. (published September 26, 1985) discloses an insect bait containing an insect-controlling material in a gelatinized starch matrix. The bait is made by coextruding starch with the insect-controlling material at temperature and pressure conditions sufficient to cook and gelatinize the starch. Alternatively, a pregelatinized starch may be mixed with the insect-controlling material and water to form a gel. In the formation of the insect bait by mixing and extruding the components, it is disclosed, it is essential to utilize additives, including the insecticides and repellants which will withstand the extrusion temperatures of starch without the degradation or vaporization. The extrusion temperatures of the insect-bait mixture, depending upon the starch content and other additives, ranges between about 160 to about 310°F at pressures of from about 300 through 800 psi.

U. S. patent no. 5,183,690 to Carr, et al. discloses a continuous process for imparting predetermined release properties to an encapsulated biologically active agent in a matrix of starchy material. The starchy material, an active agent, and water are continuously blended in an ingredient stream wherein the starchy material is at a solids concentration of at least 40%. The ingredients stream is continuously extruded as an extrudate and the extrudate is continuously recovered. The conditions of blending, extruding, and recovering are preselected to yield the predetermined release properties. The temperature is elevated to at least about 65°C to effect gelatinization of starch and assure an essentially molecular dispersion of the starch in the water. Alternatively, the core material to be encapsulated is added and blended with the aqueous dispersion of starch after the starch and water has been subjected to an elevated temperature sufficient to gelatinize the starch. In this embodiment the aqueous starch stream containing

The products of the present invention may be in the form of discrete particles, pellets, or tablets. They may be spherical in shape, curvilinear or lens-shaped, flat discs, oval shaped, or the like. The diameter of the particles may range from about 0.3 mm to about 7 mm and the l/d ratio may be from about 0.1 to about 10. The specific density of the pellets or particles may be from about 800 g/liter to about 1500 g/liter.

The total amount of plasticizer, such as water, admixed with the plasticizable matrix material, such as semolina or flour from ground cookies or ground crackers, to form a plasticized mass may range from about 20% by weight to about 50% by weight, preferably from about 25% by weight to about 45% by weight, based upon the weight of the matrix material such as semolina or flour from ground cookies or crackers. The liquid plasticizer content of the liquid encapsulant component may be at least about 35% by weight, generally at least about 50% by weight, based upon the weight of the liquid encapsulant component. The amount of the ingredient used to control the rate of release of the active component may range up to about 70% by weight, preferably from about 5% by weight to about 50% by weight, most preferably from about 10% by weight to about 35% by weight based upon the weight of the plasticizable matrix material such as semolina. The amount of the active component or encapsulant which may be encapsulated or embedded into the matrix may be from about 1% by weight to about 85% by weight, preferably from about 3% by weight to about 50% by weight, most preferably from about 5% by weight to about 30% by weight, based upon the weight of the plasticizable matrix ingredient such as semolina.

DETAILED DESCRIPTION OF THE INVENTION

A liquid encapsulant component which contains an active, sensitive encapsulant dissolved or dispersed in a liquid plasticizer is admixed with a plasticizable matrix material which is plasticizable by the liquid plasticizer to encapsulate the active encapsulant at a low temperature and under low shear conditions. Oil may be optionally added to the matrix material prior to adding the

What is claimed is:

1. A method for encapsulating or embedding a component in a matrix comprising:

a. obtaining a formable mixture by admixing ingredients comprising at least one plasticizable matrix material, a liquid encapsulant component, said liquid encapsulant component comprising an encapsulant and a liquid plasticizer, and at least one component for controlling the rate of release of the encapsulant, wherein said plasticizable matrix material is plasticizable by said liquid plasticizer at a temperature which does not substantially destroy said encapsulant, said admixing being under low shear and low temperature conditions to plasticize the plasticizable material without substantially destroying the encapsulant to obtain a substantially homogeneous plasticized, viscoelastic, formable mixture,

b. forming said formable mixture into pieces, and

c. drying said pieces,

wherein said liquid encapsulant component provides at least a substantial portion of the liquid plasticizer for forming said plasticized mixture.

2. A method as claimed in claim 1 wherein said admixing is conducted at a temperature of less than or equal to about 50°C.

3. A method as claimed in claim 2 wherein the liquid plasticizer content of said liquid encapsulant component is at least about 50 % by weight, based upon the weight of said liquid encapsulant component.

4. A method as claimed in claim 2 wherein the liquid plasticizer content of said liquid encapsulant component is sufficient to form a substantially

homogenous formable dough upon admixture of said liquid encapsulant component with said plasticizable matrix material.

5. A method as claimed in claim 4 wherein the liquid plasticizer content of said formable dough is from about 10% by weight to about 50% by weight, based upon the weight of the formable dough.

6. A method as claimed in claim 2 wherein liquid plasticizer in addition to the liquid plasticizer provided by said liquid encapsulant component is admixed with said plasticizable matrix material to obtain said formable mixture, the formable mixture is obtained in an extruder and extruded through a die without substantially expanding the formable mixture, and the extrudate is cut into pieces.

7. A method as claimed in claim 2 wherein the formable mixture is extruded to obtain an extrudate, the extrudate is cut into pieces, and the pieces are dried to a shelf-stable moisture content of less than about 10% by weight, based upon the weight of the pieces.

8. A method as claimed in claim 2 wherein said admixing to obtain said formable mixture is conducted at a pressure of from about 1 bar to about 100 bar.

9. A method as claimed in claim 2 wherein an additional encapsulant, in solid form, is admixed with said plasticizable matrix material.

10. A method as claimed in claim 9 wherein said additional encapsulant is coated with a film-forming material prior to admixing with said plasticizable matrix material.

11. A method as claimed in claim 2 wherein said formable mixture is obtained by admixing said ingredients in a continuous mixer to obtain a crumbly dough,

feeding the crumbly dough to an extruder, and plasticizing the crumbly dough into a continuous, substantially homogeneous plasticized dough in said extruder, extruding the substantially homogeneous dough through an extruder die, and cutting the extrudate into individual pieces.

12. A method as claimed in claim 1 wherein said pieces are coated with a film-forming material.

13. A method as claimed in claim 2 wherein said plasticizable matrix material comprises either semolina or flour from cookies or crackers, and said liquid plasticizer comprises water.

14. A method as claimed in claim 13 wherein said liquid encapsulant component comprises at least one member selected from the group consisting of enzymes, vitamins, micronutrients, and live microorganisms.

15. A method as claimed in claim 2 wherein said at least one release-rate controlling component is a hydrophobic component.

16. A method as claimed in claim 15 wherein said hydrophobic component is at least one member selected from the group consisting of fats, oils, waxes, fatty acids, emulsifiers, polyolefins, polyurethanes, polyvinylchloride, paraffins, polyvinyl acetates, and modified starches.

17. A method as claimed in claim 2 wherein said at least one release-rate controlling component is a high water binding capacity component.

18. A method as claimed in claim 10 wherein said high water binding capacity component is selected from the group consisting of proteins, and hydrocolloids.

19. A method as claimed in claim 2 wherein the amount of said at least one release-rate controlling agent is from about 5% by weight to about 50% by weight, based upon the weight of said plasticizable matrix material.

20. A method as claimed in claim 13 wherein the semolina or cookie flour or cracker flour content of said pieces is at least about 40% by weight, based upon the weight of said dry pieces.

21. An encapsulated product obtained by the method of claim 1 which is in substantially non-expanded, particulate form, and wherein said encapsulant is at least one heat sensitive pharmaceutical component, neutraceutical component, nutritional component, flavor component, fragrance component, or biologically active component, and said plasticizable matrix material comprises durum wheat.

22. An encapsulated product as claimed in claim 21 wherein said encapsulant comprises at least one member selected from the group consisting of enzymes, vitamins, micronutrients, and live microorganisms.

23. An encapsulated product obtained by the method of claim 1 which is in substantially non-expanded, particulate form, and wherein said encapsulant is at least one heat sensitive pharmaceutical component, neutraceutical component, nutritional component, flavor component, fragrance component, or biologically active component, and said plasticizable matrix material comprises ground cookies or ground crackers.

24. An encapsulated product as claimed in claim 23 wherein said encapsulant comprises at least one member selected from the group consisting of enzymes, vitamins, micronutrients, and live microorganisms.

25. An encapsulated product obtained by the method of claim 1 wherein said encapsulant is at least one member selected from the group consisting of: acepromazine acetaminophen, acetohexamide, acetohydroxamic acid, acetycholine, acetylcysteine acyclovir, albendazole, alclometasone dipropionate , allopurinol, alprazolam, alprostadil, amcinoide, amantadine, amdinocillin, amikacin amiloride, aminocaproic acid, aminophylline, aminosalicylate , aminosalicyllic acid, amitriptyline hydrochloride, ammonium chloride, amobarbital, amodiaquine hydrochloride, amoxapine, amoxicillin, amphetamine sulfate, amphotericin, ampicillin amprolium, acetazolamide acetyldigoxin, acetylsalicylic acid, anileridine, anthraline, antipyrine, antivenin, apomorhine, apraclonidine, ascorbic acid, aspirin, acromycin atropine, amoxycillin anipamil, azaperone azatadine maleate, azathioprine, azithromycin, aztreonam, bacampicillin, bacitracin, baclofen, barium salts, beclomethasone diproionate, belladonna extract, bendroflumethiazide, benoxinate hydrochloride, benzethonium chloride , benzocaine, benzonatate benzthiazide, benztropine mesylate, betain, betamethasone, betaxolol , betanechol chloride, biotin, biperiden, bisacodyl, bismuth, botulism antitoxin, bromocriptine mesylate, bromodiphenhydramine hydrochloride, bumetanide, bupivacaine, busulfan butabarbital sodium,butalbital, combinations of butalbital, caffeine and aspirin and codeine, beta-carotene, calcifediol, calcium carbonate, calcium citrate, calcium salts, candicidin, captopril, carbachol, carbamazepine, carbenicillin indanyl sodium, carbidopa, carbinoxamine maleate, carboprost tromethamine, carboxymethylcellulose, carisoprodol, casanthranol, cascara, castor oil, cefaclor, cefadroxil, cefamandole nafate, cefazolin, cefixime, cefoperazone, cefotaxime, cefprozil, ceftazidime, cefuroxime axetil, cephalexin, cephradine, chlorambucil, chloramphenicol, chlordiazepoxide, chloroquine phosphate, chlormadinone acetate, chlorothiazide, chlorpheniramine maleate, chloroxylenol, chlorpromazin, chlorpropamide, chlorprothixene, chlorprothixene, chlortetracycline bisulfate, chlortetracycline hydrochloride, chlorthalidone, chlorzoxazone, cholecalciferol, cholera vaccine, chromic chloride, chymotrypsin, cimetidine, cinoxazin, cinoxate, ciprofloxacin,

cisplatin, clarithromycin, clavulanate potassium, clemastine fumarate, clidinium bromide, clindamycin hydrochloride, -palmitate and -phosphate, clioquinol, clofazimine, clofibrate, clomiphene citrate, clonazepam, cinnarizine, clonidine hydrochloride, clorsulon, clotrimazole, cloxacillin sodium, cyanocobalamin, cocaine, coccidioidin, cod liver oil, codeine, colchicine, colestipol, corticotropin, corisone acetate, cyclacillin, cyclizine hydrochloride, cyclobenzaprine hydrochloride, cyclophosphamide, cycloserine, cyclosporine, cyproheptadine hydrochloride, cysteine hydrochloride, danazol, dapsone, dehydrocholic acid, demeclocycline, desipramine, desoximetasone, desoxycorticosterone acetate, dexamethasone, dexchlorpheniramine maleate, Dexpanthenol, dextroamphetamine, dextromethorphan, diazepam, diazoxide, dibucaine, dichlorphenamide, dicloxacillin sodium, dicyclomine, dienestrol, diethylpropion hydrochlorid, diethylstilbestrol, diflunisal, digitalis, dicoumarol, digitoxin, digoxin, dihydroergotamine, dihydrostreptomycin, dihydrotachysterol, dihydroxyaluminium aminoacetate, dihytoxyaluminium sodium carbonate, diltiazem hydrochloride, dimenhydrinate, dimercaprol, diphenhydramine hydrochloride, diphenoxylate hydrochloride, diphteria antitoxin, dipyridamole, disopyramide phosphate, disulfiram, dobutamine hydrochloride, docusate calcium, docusate sodium, dopamine hydrochloride, doxepin hydrochloride, doxycycline, doxycycline hyclate, doxylamine cuccinate, dronabinol, droperidol, drotaverine, dydrogesterone, dyphylline, guaifenesin, enalapril maleate, analaprilat, ephedrine, epinephrine, equilin, ergocalciferol, ergoloid mesylates, ergonovine maleate, ergotamine tartrate, erythrityl tetranitrate, erythromycin, estradiol, estriol, estrogene, estrone, estropipate, ethcrynic acid, ethambutol hydrochlorid, ethchlorvynol, ethinyl estradiol, ethionamide, ethopropazine hydrochloride , ethotoin, ethynodiol diacetate, etidronate disodium, etoposide, eugenol, famotidine, fenoprofen, ferrous fumatate, ferrous gluconate, ferrous sulfate, flucytosine, fludrocortisone acetate, flunisolide, fluocinolone acetonide, fluocinonide, fluorescein sodium, fluorometolone, fluorouracil, fluoxymesterone, fluphenazine, flurandrenolide, flurazpam, flurbiprofen, folic acid, furazolidone,

flunitrazepam, furosemide, gemfibrozil, gentamicin, gentian violet, glutarate, glutethimide, glycopyrrolate, chorionic gonadotropin,gramicidin, griseofulvin, guaifenesin, guanabenz, guanadrelsulfate, halazone, haloperidol, haloprogin, halothane, heparin calcium, hepatitis virus vaccine, hetacillin potassium, hexylresorcinol, histamine phosphate, histidine, homatropine, histoplasmin, hydralazine hydrochloride, hydrochlorothiazide, hydrocodone bitartrate, hydrocortisone, hexobarbital, hydroflumethiazide, hydromorphone hydrochloride, hydroquinone, hydroxocobalamin, hydroxyamphetamine, hydroxychloroquine sulfate, hydroxyprogesterone caproate, hydroxyurea, hydroxine hydrochloride, hydroxine pamoate, hyoscyamine, hyoscyamine sulfate, ibuprofen, ifosfamide, imipramide, imipramide hydrochloride, indapamide, indomethacin, insulin, inulin, iocetamid, iodoquinol, iohexol, iopamidol, ipecac, ipodate calcium, ipodate sodium, isocarboxacid, isoetharine hydrochloride, isoflurane,isoniacid, isopropamide iodine, isoproterenol hydrochloride, isosorbide dinitrate, isotretenoin, isoxsuprine hydrochloride, kanamycin sulfate, ketoprofen, ketoconazole, labetalol hydrochloride, lanolin, leucine, leucovorin calcium, levamisole hydrochloride, levocarnithine, levodopa, levonorgestrel, levorphanol tartrate, levothyroxine sodium, lidocaine, lincomycin hydrochloride, lindane, liothyronine sodium, liotrix, lisinopril, lithium carbonate, loperamide hydrochloride, loracarbef, lonetil, lorazepam, lovastatin, loxapine, lysine, mafenide acetate, magaldrte, magnesium carbonate, magnesiumchloride, magnesium gluconate, magnesium oxide, other magnesium salts, malathinon, manganese salts, manganese, maprotiline hydrochloride, mazindol, measle virus vaccine, mebendazole, mebrofenin, mecamylamine hydrochloride, meclizine hydrochloride, meclocycline , meclofenamate sodium, medroxyprogesterone acetate, mefenamic acid, megestrol acetate, meglumine, melphalan, menadiol sodium diphosphate, menadione, menotropine, meperidine, mephenytoin, mephobarbital, meprednisone, meprobamate, mercaptopurine, mesoridazine besylate, mestranol, metaproterenol sulfate, metaraminol bitartrate, methacycline hydrochloride, methadone hydrochloride, methamphetamine hydrochloride,

methazolamide, methdilazine, methenamine, methicillin sodium, methimazole, methionine, methocarbamol, methotrexate, methoxsalen, methoxyflurane, methsuximide, methyclothiazide, methylbenzethonium chloride, methyldopa, methylergonovine maleate, methylphenidate hydrochloride, methylprednisolone, methyltestosterone, methysergide maleate, metoclopramide, metolazone, meoprolol tartrate, metronidazole, metyrapone, metyrosine, mexiletine hydrochloride, mexiletine hydrochloride, miconazole, minocycline hydrochloride, minoxidil, mitomycin, mitotane, molindone hydrochloride, monobenzone, morphine sulfate, mupirocin, medazepam, mefruside, methandrostenolone, methylsulfadiazine, nadolol, nafcillin, nafcillin sodium, nalidixic acid, nalorphine, naloxone, nandrolone decanoate, nandrolone phenpropionate, naproxen, natamycin, neomycin, neomycin sulfate, neostimine bromide, niacin, nitrofurantoin nalidixic acid, nifedipine, nitrazepam, nitrofurantoin, nitroglycerine, nitromerson, nizatidine, nonoxynol 9, norethindrone, norethindrone acetate, norfloxacin, norgestrel, nortriptyline hydrochloride, noscapine, novobiocin sodium, nystatin, opium, oxacillin sodium, oxamniquine, oxandrolone, oxazepam, oxprenolol hydrochloride, oxtriphylline, oxybenzone, oxybutynin chloride, oxycodone hydrochloride, oxycodone, oxymetazoline hydrochloride, oxymetholone, oxymorphone hydrochloride, oxyphenbutazone, oxytetracycline, padimate, panreatin, pancrelipase, papain, panthenol, papaverin hydrochloride, parachlorophenol, paramethasone acetate, paregoric, paromomycin sulfate, penicillamine, penicillin, penicillin derivatives, pentaerythritol tetranitrate, pentazocine, pentazocine hydrochloride, pentazocine salts, pentobarbital sodium, perphenazine, pertussis, phenacemide, phenazopyridine hydrochloride, phendimetrazine tartrate, phenelzine sulfate, phenmetrazine hydrochloride, phenobarbital, phenophtalein, phenoxybenzamine hydrochloride, phentermine hydrochloride, phenylalanine, phenylbutazone, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, physostigmine, phytonadione, pilocarpine , pimozide, pindolol, piperazine, piroxicam plicamycin, poliovirus vaccine inactivated, polycarbophil, polymyxin b sulfate, polythiazide, potassium chloride,

potassium citrate, potassium cluconate, potassium iodine, potassium sodium tartrate, povidone iodine, pralidoxime chloride, pramoxine hydrochloride, pramezam, prazepam, praziquantel, prazosin hydrochloride, prazosin hydrochloride, prednisolone, prilocaine, primaquine, primidone, probenecid, probucol, procainamide hydrochlorid, procaine hydrochlorjde, procarbacine hydrochloride, prochlorperazine, prochlorperazine maleate, procyclidine hydrochloride, progesterone, proline, promazine, promazine hydrochloride, promazine, promethazine, promethazine hydrochloride, propafenone hydrochloride, propantheline, proparacaine hydrochloride, propoxycaine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, propanolol hydrochloride, propyliodone, propylthiouracil, propylthiouracil, protriptyline hydrochloride, pseudoephedrine hydrochloride, pumice, pyrantel pamoate, pyrazinamide, pyrethrum extract, pyridostigmine bromide, pyridoxine hydrochloride, pyrilamine maleate, pyrimethamine, pyroxylin, pyrvinium pamoate, phenacetin, phenytoin, prednisone, uinidine gluconate, quinidine sulfate, rabies vaccine, racepinephrine ranitidine, rauwolfia serpentina, resorcinol, ribavirin, riboflavin, rifampin, ritodrine, rubella virus vaccine, saccharin, saccharin sodium, salicylamide, salicylic acid, salsalata, scopolamine, secobarbital sodium, selenius acid, selenium sulfate, sennaserine, simethicone, sodium ascorbate, sodium bicarbonate, sodium fluoride, sodium gluconate, sodium iodide, sodium lactate, sodium nitrite, sodium ditroprusside, sodium salicylate, spironolactone, stannozolol, streptomycin, sucralfate, sulfacetamide, sulfadiazine, reserpine, sulfadioxine, sulfamerazine, sulfamethazine, sulfamethizole, sulfamethoxazole, sulfamethoxydiazine, sulfapyridin, sulfasalazine, sulfaperin, sulfathiazole, sulfisoxazole, sulfinpyrazone, sulindac, suprofen, stilains, tamoxifen citrate, temacepam, terbutaline sulfate, terfenadine, terpin, testolacton, testosterone, tolazamide, tolbutamide, tetracaine, tetracycline, tetrahydrocycline, theophylline, thiabendazole, thiamine hydrochloride, thiamin, thiamylal, thiethylperazine thimerosal, thioguanine , thioridazine hydrochloride, thistrepton, thiotepa, thiothixene, threonine, thyroid, ticarcillin, timolol, tioconazole,

titaniumdioxide, tolazamide, tolbutamide, tolmetin, tolnaftate, trazodone hydrochloride, tretinoin, triacetin, triamcinolone, triamterene, triazolam, trichorfon, trichlormethiazide, trientine hydrochloride, trifluoperazine hydrochloride, triflupromazine, trihexyphenidyl hydrochloride, trimeprazine tartrate, trimethadione, trimethobenzamide hydrochloride, trimethoprim, trioxsalen, tripelennamine, triprolidine, trisulfapyrimidine, tropicamide, trypsin, tryptohan, tuberculin, tyloxapol, tyropanoate sodium, tyrosine, tyrothricin, thyrothricin bethamethasone, thiotic acid, sotalol, salbutamol, norfenefrine, silymarin, dihydroergotamine, buflomedil, etofibrate, indometacin, urea, valine, valproic acid, vancomycin hydrochloride, vasopressin, verapramil, vidarabine, vinblastine, vincristine, vitamins, warfarin, yellow fever vaccine, zinc acetate, zinc carbonate, zinc chloride, zinc gluconate, beta acetyl digoxin, piroxicam, haloperidol, ISMN, amitriptylin, diclofenac, nifedipine, verapamil, pyritinol, nitrendipin, doxycycline, bromhexine, methylprdnisolone, clonidine, fenofibrate, allopurinol, pirenyepine, levothyroxin, tamoxifen, metildigoxin, o-(beta-hydroxyethyl)-rutoside, propicillin, aciclovir mononitrate, paracetamol, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxin, tramadol, bromocriptine, loperamide, ketotifen, fenoterol, cadobelisate, propanolol, enalaprilhydrogen maleate, bezafebrate, ISDN, gallopamil, xantinol nicotinate, digitoxin, flunitrazepam, bencyclane, dexapanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylpenicillin, furosemide, bromazepam, flunarizin, erythromycin, metoclopramide, acemetacin, ranitidin, biperiden, metamizole, doxepin, dipotassium chloroazepate, tetrazepam, estramustine phosphat, terbutaline, captopril, maprotiline, prazosin, atenolol, glibenclamide, cefaclor, etilfrine, cimetidine, theophylline, hydromorphone, ibuprofen, primidone, clobazam, oxaceprol, medroxyprogesterone, flecainid, pyridoxal 5 phosphat glutaminate, hymechromone, etofylline clofibrate, vincamine, cinnarizine, diazepam , ketoprofen, flupentixol, molsimine, glibornuride, dimetinden, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine, glisoxepide, kallidinogenase, oxyfedrine, baclofen, carboxymethylcysteine,

thioridazine, betahistine, L-tryptophan, murtol, bromelaine, prenylamine, salazosulfapyridine, astemizol, sulpiride, benzerazide, dibenzepine, acetylsalicylic acid, miconazol, nystatin, ketoconazole, sodium picosulfate, coltyramine, gemfibrocil, rifampicin, fluocortolone, mexiletin, amoxicillin, terfenadrin, mucopolysaccharide polysulfade, triazolam, mianserin, tiaprofenic acid, amezinium metilsulfate, mefloquine, probucol, quinidine, carbamazepine, L-aspartate, penbutolol, piretanide, aescin amitriptyline, cyproterone, sodium valproinate, mebeverine, bisacodyl, 5-aminosalicylic acid, dihydralazine, magaldrate, phenprocoumon, amantadine, naproxen, carteolol, famotidine, methyldopa, auranofine, estriol, nadolol, levomepromazine, doxorubicin, medofenoxate, azathioprine, flutamide, norfloxacin, fendiline, and prajmalium bitartrate.

26. An encapsulated product obtained by the method of claim 1 wherein said encapsulant is at least one member selected from the group consisting of antioxidants, phytochemicals, hormones, vitamins, pro-vitamins, minerals, microorganisms, prebiotics, probiotics, trace elements, essential and/or highly unsaturated fatty acids, antibiotics, nutritional supplements, enzymes, formulations containing zidovudine, macromolecular polypeptides, aromatic nitro and nitroso compounds and their metabolites useful as anti-viral and anti tumor agents, HIV protease inhibitors, antibiotics, viruses, pigments, steroids, oligopeptides, dipeptides, amino acids, flavor components, fragrance components, detergents and surface-active components, lipid derivatives of phosphonatides, amphiphilic polymers, adenosine derivatives, sulfated tannins, monoclonal antibodies, and metal complexes of water-soluble texathyrin.

27. An encapsulated product obtained by the method of claim 1 wherein said encapsulant is at least one member selected from the group consisting of amylases, proteases, lipases, pectinases, cellulases, hemicellulases, pentosanases, and phytases.

28. A food composition comprising an encapsulated product obtained by the method of claim 1 which is selected from the group consisting of ready-to-eat breakfast cereals, snacks, soups, salads, cakes, cookies, crackers, puddings, ice creams, yogurts, puddings, custards, baby foods, medicinal foods, sports bars, and beverages.

29. A food topping comprising an encapsulated product obtained by the method of claim 1 in granular form.

30. A method for encapsulating or embedding a component in a matrix comprising:

a. obtaining a formable mixture by admixing ingredients comprising at least one plasticizable matrix material comprising a durum ingredient, a liquid plasticizer, an encapsulant, and an additional component selected from the group consisting of at least substantially non-gelatinized starch, carbohydrates which have a lower molecular weight than starches, fiber, cellulose, or hemi-cellulose for controlling the rate of release of the encapsulant, wherein said plasticizable matrix material is plasticizable by said liquid plasticizer at a temperature which does not substantially destroy said encapsulant, said admixing being under low shear and low temperature conditions to plasticize the plasticizable material without substantially destroying the encapsulant to obtain a substantially homogeneous plasticized, viscoelastic, formable mixture,

b. forming said formable mixture into pieces, and

c. drying said pieces.

31. A method as claimed in claim 30 wherein said at least one additional component increases the penetratability or porosity of the matrix to permit quicker release of the encapsulant from the matrix.

32. A method as claimed in claim 30 wherein said at least one additional component comprises a sugar or a starch hydrolyzate.

33. A method as claimed in claim 30 wherein said at least one additional component comprises an at least substantially non-gelatinized starch.

34. A method as claimed in claim 30 wherein said durum ingredient comprises semolina.

35. A method as claimed in claim 30 wherein a liquid encapsulant component which contains an active, sensitive encapsulant dissolved or dispersed in a liquid plasticizer is admixed with said at least one plasticizable matrix material.

36. A method as claimed in claim 30 wherein said admixing is conducted at a temperature of less than or equal to about 50°C.

37. A method as claimed in claim 30 wherein an additional encapsulant, in solid form, is admixed with said plasticizable matrix material.

38. A method as claimed in claim 30 wherein said encapsulant is coated with a film-forming material prior to admixing with said plasticizable matrix material.

39. A method as claimed in claim 30 wherein said encapsulant comprises at least one member selected from the group consisting of enzymes, vitamins, micronutrients, and live microorganisms.

40. A method as claimed in claim 30 wherein an oil or fat is admixed with said plasticizable matrix material for controlling the rate of release of said encapsulant from the matrix.

41. A method for encapsulating or embedding a component in a matrix comprising:

a. obtaining a formable mixture by admixing ingredients comprising at least one plasticizable matrix material, a liquid plasticizer, an encapsulant, a matrix component which is substantially non-plasticizable at temperatures lower than the decomposition temperature of the encapsulant, and at least one component for controlling the rate of release of the encapsulant, wherein said plasticizable matrix material is plasticizable by said liquid plasticizer at a temperature which does not substantially destroy said encapsulant, said admixing being under low shear and low temperature conditions to plasticize the plasticizable material without substantially destroying the encapsulant to obtain a substantially homogeneous plasticized, viscoelastic, formable mixture,

b. forming said formable mixture into pieces, and

c. drying said pieces.

42. A method as claimed in claim 41 wherein the substantially non-plasticizable matrix component is selected from the group consisting of at least substantially non-gelatinized starch, carbohydrates which have a lower molecular weight than starches, fiber, cellulose, and hemi-cellulose.

43. A method as claimed in claim 41 wherein the substantially non-plasticizable matrix component comprises an at least substantially non-gelatinized

starch, said plasticizable matrix material comprises semolina, and said at least one component for controlling the rate of release of the encapsulant comprises a fat or oil.

44. A method as claimed in claim 41 wherein a liquid encapsulant component which contains said encapsulant dissolved or dispersed in said liquid plasticizer is admixed with said at least one plasticizable matrix material.

45. A method as claimed in claim 44 wherein said encapsulant component comprises at least one member selected from the group consisting of enzymes, vitamins, micronutrients, and live microorganisms.

46. An edible product for human or animal consumption comprising an encapsulated product, said encapsulated product being obtained by admixing at least one plasticizable matrix material, a liquid plasticizer, an encapsulant, a matrix component which is substantially non-plasticizable at temperatures lower than the decomposition temperature of the encapsulant, and at least one component for controlling the rate of release of the encapsulant, wherein the substantially non-plasticizable matrix component comprises an at least substantially non-gelatinized starch, said plasticizable matrix material comprises at least one member selected from the group consisting of high gluten content flours, gluten from wheat, durum wheat, durum semolina, pregelatinized starch, pentosans, hydrocolloids, and mixtures thereof, and said encapsulant comprises at least one member selected from the group consisting of enzymes, vitamins, micronutrients, and live microorganisms.

AMENDED CLAIMS

[received by the International Bureau on 29 March 2000 (29.03.00); original claims amended; new claims 47-62 added, remaining claims unchanged (4 pages)]

47. A method as claimed in claim 1 wherein the formable mixture is extruded through a die having multiple apertures, at a rate of extrudate per die area of less than about 5 kg/h per mm^2.

48. A method as claimed in claim 47, wherein the rate of extrudate per die area is less than 3 kg/h per mm^2.

49. A method as claimed in claim 48, wherein the rate of extrudate per die area is less than about 0.5 kg/h per mm^2.

50. A method as claimed in claim 47, wherein the diameter of the apertures is from about 0.3 mm to about 5 mm.

51. A method as claimed in claim 50, wherein the diameter of the apertures is from about 0.5 mm to about 1 mm.

52. A method as claimed in claim 30 wherein the formable mixture is extruded through a die having multiple apertures to obtain an extrudate at a rate of extrudate per die area of less than about 5 kg/h per mm^2.

53. A method as claimed in claim 52, wherein the rate of extrudate per die area is less than 3 kg/h per mm^2.

54. A method as claimed in claim 53, wherein the rate of extrudate per die area is less than about 0.5 kg/h per mm^2.

55. A method as claimed in claim 52, wherein the diameter of the apertures is from about 0.3 mm to about 5 mm.

56. A method as claimed in claim 55, wherein the diameter of the apertures is from about 0.5 mm to about 1 mm.

57. A method as claimed in claim 41 wherein the formable mixture is extruded through a die having multiple apertures to obtain an extrudate at a rate of extrudate per die area of less than about 5 kg/h per mm^2.

58. A method as claimed in claim 57, wherein the rate of extrudate per die area is less than 3 kg/h per mm^2.

59. A method as claimed in claim 58, wherein the rate of extrudate per die area is less than about 0.5 kg/h per mm^2.

60. A method as claimed in claim 57, wherein the diameter of the apertures is from about 0.3 mm to about 5 mm.

61. A method as claimed in claim 60, wherein the diameter of the apertures is from about 0.5 mm to about 1 mm.

62. A method for encapsulating or embedding a component in a matrix comprising:

a. obtaining a formable mixture by admixing ingredients comprising at least one plasticizable matrix material, an encapsulant, a liquid plasticizer, and a substantially non-gelatinized starch for controlling the rate of release of the encapsulant, wherein said plasticizable matrix material is plasticizable by said liquid plasticizer at a temperature which does not substantially destroy said encapsulant, said admixing being under low shear and low temperature conditions to plasticize the plasticizable material without substantially destroying the encapsulant to obtain a substantially homogeneous plasticized, viscoelastic, formable mixture,

b. forming said formable mixture into pieces by extruding the formable mixture through a die having multiple apertures

at a rate of extrudate per die area of less than about 5 kg/h per mm^2, and

c. drying said pieces.